

M. Moreno-Mañas* and M. Teixidó

Department of Chemistry, Universidad Autónoma de Barcelona,
Bellaterra, 08193-Barcelona, Spain
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2,3-Diaryl-1,4-diazolyl-2,3-epoxybutanes have been prepared from dimethylstilbenes. An efficient although neglected synthesis of the required olefins has been recovered from the literature. The target compounds show moderate antifungal activity.

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Introduction.

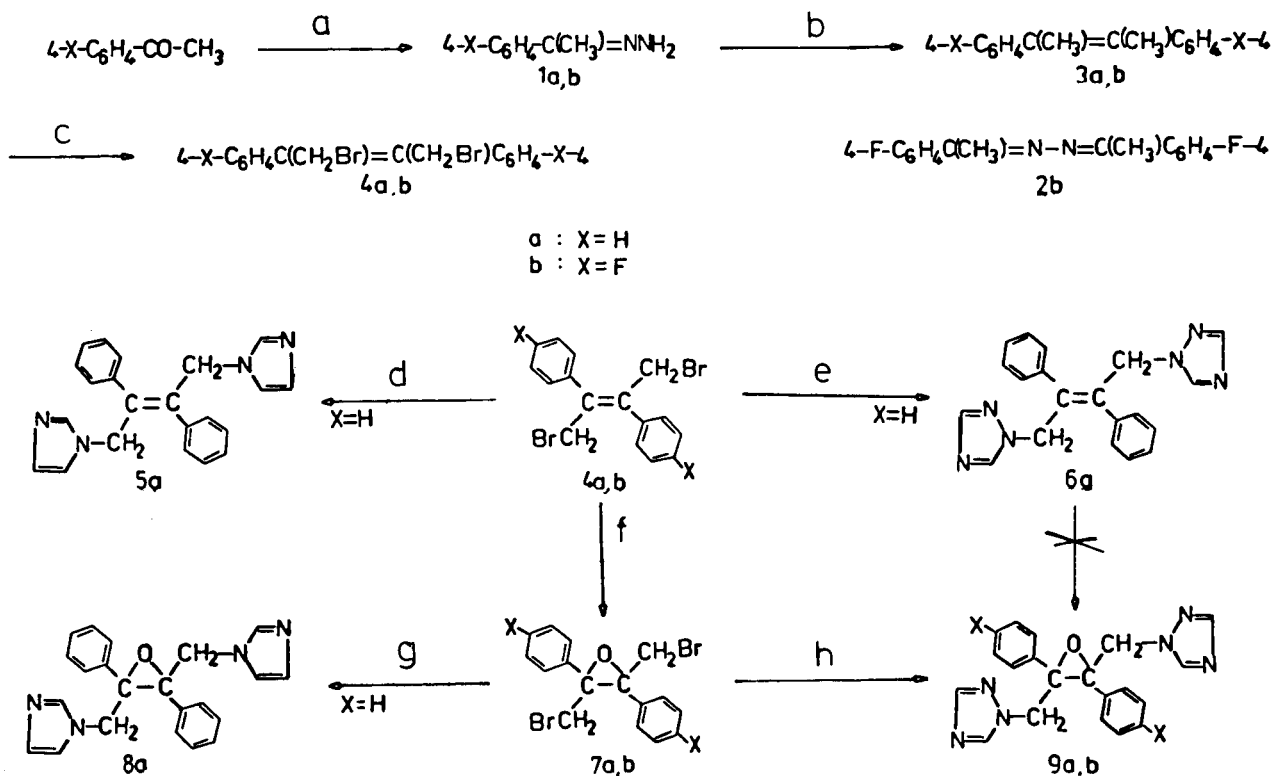
Imidazole and triazole derivatives constitute the most important family of compounds used against fungal infections. Among them, those containing two vicinal carbon atoms bearing a first oxidation degree function have attracted a great deal of attention [1].

During the last few years we have been involved in a continuing effort to develop potent antifungal agents [2,3]. As a continuation of our previous work we wanted to synthesize molecules of the title type to perform biological evaluations with them.

Results.

The synthetic pathway is shown in the Scheme. The required stilbenes **3a,b** are better prepared by an efficient and long neglected method first described by Vargha and Kovács [4] and later modified by Simamura *et al.* [5]. Thus, treatment of acetophenone and 4-fluoroacetophenone hydrazones, **1a** and **1b**, with lead (IV) oxide followed by sulphur dioxide produces 2,3-diphenyl-2-butene, **3a**, and 2,3-bis(4-fluorophenyl)-2-butene, **3b**, as *Z,E* mixtures. Small amounts of the corresponding azine, **2b** were also isolated in the second case. The formation of both isomers

Scheme



(a) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, ethanol, refl. (b) PbO_2 , benzene followed by SO_2 stream. (c) NBS, tetrachloromethane, $h\nu$. (d) Imidazole, dichloromethane, refl. (e) 1,2,4-Triazole, potassium carbonate, butanone, imidazole, DME, refl. (f) *m*-chloroperbenzoic acid, chloroform, refl. (g) sodium acetate, DME, refl. (h) 1,2,4-Triazole, potassium carbonate, acetonitrile, refl.

is not a serious drawback since other methods also produce both isomers and isomerization takes place in the next step: bromination with NBS in carbon tetrachloride.

The dibromoderivatives **E-4a,b** were used to introduce the heterocyclic moieties. Treatment of **E-4a** with excess imidazole in dichloromethane afforded **E-1,4-di(imidazol-1-yl)-2,3-diphenyl-2-butene**, **5a** in 76% yield. Treatment of **4a** with 1,2,4-triazole in butanone and in the presence of potassium carbonate afforded **E-2,3-diphenyl-1,4-di(1,2,4-triazol-1-yl)-2-butene**, **6a**, in 90% yield. However, compound **6a** could not be converted into the oxirane **9a** under a variety of conditions (*m*-chloroperbenzoic acid (MCPBA) in dichloromethane, peracetic acid in dichloromethane and aqueous sodium hypochlorite/pyridine).

The bromostilbenes **E-4a,b** were converted into the *trans* oxiranes **7a,b** by treatment with MCPBA in chloroform in 94 and 98% yield respectively. The oxirane **7a** was finally converted into *trans*-2,3-epoxy-1,4-di(imidazol-1-yl)-2,3-diphenylbutane, **8a**, in 57% yield by reaction with the sodium salt of imidazole generated with sodium hydride in dimethoxyethane. Also, **7a**, afforded *trans*-2,3-epoxy-2,3-diphenyl-1,4-di(1,2,4-triazol-1-yl)butane, **9a**, in 37% yield by treatment with 1,2,4-triazole and potassium carbonate in acetonitrile. The oxirane **7b** was similarly converted into **9b** in 64% yield.

The pmr spectra of compounds **6** and **9** show two different singlets for the 1,2,4-triazole protons, thus excluding the possibility of isomers substituted at N-4.

Compounds **5**, **6**, **8** and **9** showed a moderate antifungal activity.

EXPERIMENTAL

The ir spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. The pmr spectra were recorded on a Bruker WP80SY spectrometer. The ms were run on a Hewlett-Packard 5985-B spectrometer; only peaks with intensity higher than 20% are reported unless they belong to molecular ions or to very significant fragments.

2,3-Diphenyl-2-butene (**3a**).

A mixture of acetophenone (40.8 g, 0.34 mole), 98% hydrazine hydrate (69 ml, 1.36 moles of hydrazine) and ethanol (150 ml) was refluxed for 6 hours. Part of the solvent was evaporated at reduced pressure and the residue was partitioned between water and dichloromethane. The organic layer was dried and evaporated to afford acetophenone hydrazone, **1a**, as an unstable yellow oil (100% yield); pmr (deuteriochloroform): δ 2.1 (s, 3H), 5.4 (broad s, 2H), 7.0-7.5 (m, 3H), 7.5-7.8 (m, 2H).

Lead (IV) oxide (50 g) was added portionwise with stirring to **1a** (5.0 g, 0.036 mole) in benzene (250 ml). The stirring was continued for 3 hours until the colour changed from yellow to red. The mixture was filtered and a stream of sulphur dioxide was passed through the clear solution until decoloration. The solvent was evaporated to afford a mixture of *Z* and **E-3a**. Recrystallization in ethanol afforded pure **E-3a**, mp 107° (lit [5] mp 107°).

2,3-Bis(4-fluorophenyl)-2-butene (**3b**).

This compound was prepared in a similar manner (63% yield) as for

3a. 4-Fluoroacetophenone hydrazone, **1b**, was an oil (87%); pmr (deuteriochloroform): δ 2.0 (s, 3H), 5.33 (broad s, 2H), 6.9 (dd, *J* = 9 and 9 Hz, 2H), 7.5 (dd, *J* = 9 and 6 Hz, 2H).

E-3b.

This compound had mp 115-116°; ir (potassium bromide): 1400, 1220, 840 cm^{-1} ; pmr (deuteriochloroform): 1.86 (s, 6H), 6.9-7.2 (m, 8H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{14}\text{F}_2$: C, 78.67; H, 5.77. Found: C, 78.72; H, 5.82.

Z-3b.

This compound had mp 52-54°; ir (potassium bromide): 1600, 1490, 1210, 830 cm^{-1} ; pmr (deuteriochloroform): δ 2.15 (s, 6H); 6.67-6.97 (m, 8H).

In this operation a small amount of 4-fluoroacetophenone azine, **2b**, was isolated, mp 127-129°; ir (potassium bromide): 1600, 1500, 1230, 840 cm^{-1} ; pmr (deuteriochloroform): δ 2.33 (s, 6H), 7.09 (dd, *J* = 8.5 and 8.5 Hz, 4H), 7.91 (dd, *J* = 8.5 and 6 Hz, 4H); ms: 272 (M, 38), 257 (100), 136 (35), 122 (22), 121 (30), 95 (63), 75 (33).

Anal. Calcd. for $\text{C}_{16}\text{H}_{14}\text{F}_2\text{N}_2$: C, 70.58; H, 5.18; N, 10.29. Found: C, 70.67; H, 5.44; N, 10.25.

1,4-Dibromo-2,3-bis(4-fluorophenyl)-2-butene (**4b**).

A mixture of **3b** (1.0 g, 4.1 mmoles), *N*-bromosuccinimide (1.55 g, 8.7 mmoles) and carbon tetrachloride (30 ml) was irradiated for 1 hour with a 500W white light bulb. After cooling, the mixture was filtered and the filtrate was evaporated to afford 8.3 g (98%) of a mixture of isomers **4b**. The *E* isomer was isolated by recrystallization in ethanol, mp 170-175° dec; ir (potassium bromide): 1600, 1500, 1220, 1150, 840 cm^{-1} ; pmr (deuteriochloroform): δ 4.0 (s, 4H), 7.0-7.5 (m, 8H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{Br}_2\text{F}_2$: C, 47.79; H, 3.01; Br, 39.75. Found: C, 48.89; H, 2.96; Br, 39.26. In spite of repeated recrystallizations the elemental analysis could not be improved.

Mixtures enriched in **Z-4b** allowed the determination of its chemical shifts: pmr (deuteriochloroform): δ 4.37 (s, 4H), 6.7-7.2 (m, 8H).

1,4-Dibromo-2,3-diphenyl-2-butene (**4a**).

This compound was obtained in a similar manner (98% yield) as for **4b**. The *E* isomer was isolated by recrystallization in ethanol, mp 147-150° (lit [6] mp 153-155°); pmr (deuteriochloroform): δ 4.1 (s, 4H), 7.5 (deceptive s, 10H). Mixtures enriched in **Z-4a** allowed the determination of its chemical shifts: pmr (deuteriochloroform): δ 4.6 (s, 4H), 7.2 (deceptive s, 10H).

1,4-Di(imidazol-1-yl)-2,3-diphenyl-2-butene (**5a**).

A mixture of **E-4a** (2.34 g, 6.39 mmoles), imidazole (2.0 g, 29.5 mmoles) and dichloromethane (56 ml) was refluxed for 5 hours and then extracted with water. The organic layer was dried and evaporated to afford 1.66 g (76% yield) of crude **5a**, mp 186-188° (from ethanol); ir (potassium bromide): 1450, 1290, 1220, 1070, 770 cm^{-1} ; pmr (deuteriochloroform): δ 4.6 (s, 4H), 6.53 (s, 2H), 6.93 (s, 2H), 7.0-7.15 (m, 6H), 7.25-7.5 (m, 6H); ms: 341 (M+1, 12), 272 (17), 271 (48), 260 (21), 259 (100), 205 (50), 204 (28), 203 (32), 202 (23), 191 (19), 190 (20), 189 (19), 178 (22), 165 (17), 128 (20), 127 (19), 115 (28), 103 (29), 91 (22), 82 (23), 81 (56), 77 (54), 54 (33).

Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{N}_4$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.65; H, 5.90; N, 16.66.

2,3-Diphenyl-1,4-di(1,2,4-triazol-1-yl)-2-butene (**6a**).

A solution of compound **4a** (1.36 g, 3.7 mmoles) in butanone (50 ml) was added dropwise during 2 hours over an stirred mixture of 1,2,4-triazole (0.56 g, 8.2 mmoles), potassium carbonate (1.13 g, 8.2 mmoles) and refluxing butanone (20 ml). The reflux was additionally kept for 15 minutes. After cooling the mixture was filtered and the solution evaporated to afford a brown solid which was washed with ethanol to afford **6a** as a white solid (1.14 g, 90% yield), mp 211-214°; ir (potassium bromide): 1500, 1270, 1200, 1140, 710 cm^{-1} ; pmr (deuteriochloroform): δ 4.90 (s, 4H), 7.2-7.45 (m, 10H), 7.60 (s, 2H), 7.90 (s, 2H); cmr (deuteriochloroform): δ 53.13, 128.39, 128.93, 136.81, 137.42, 143.46, 151.94; ms: 342 (M, 8), 272 (39), 260 (89), 218 (27), 206 (24), 205 (23), 204 (100), 203

(70), 202 (31), 196 (35), 191 (46), 189 (34), 178 (30), 165 (22), 143 (31), 115 (30), 103 (23), 77 (22).

Anal. Calcd. for $C_{20}H_{18}N_6$: C, 70.16; H, 5.29; N, 24.54. Found: C, 70.23; H, 5.40; N, 24.47.

trans-1,4-Dibromo-2,3-epoxy-2,3-bis(4-fluorophenyl)butane (**7b**).

A solution of **E4b** (4.6 g, 11.0 mmoles) in chloroform (65 ml) was added dropwise on a solution of *m*-chloroperbenzoic acid (4.92 g, 30 mmoles) in chloroform (110 ml). The mixture was then refluxed for 12 hours. After cooling the solution was washed with aqueous sodium sulfite, with aqueous sodium bicarbonate and finally with water, dried and evaporated to afford 4.7 g (98% yield) of **7b**, mp 125-127° (from ethanol); ir (potassium bromide): 1610, 1510, 1240-1230, 840 cm^{-1} ; pmr (deuteriochloroform): δ 3.10 (d, J = 10 Hz, 2H), 3.47 (d, J = 10 Hz, 2H), 6.9-7.2 (m, 4H), 7.3-7.7 (m, 4H); cmr: δ 35.99, 71.35, 115.07 and 116.15 (d, J = 20 Hz), 129.06 and 129.47 (d, J = 7 Hz), 130.77 and 130.95 (d, J = 3 Hz), 156.65 and 168.98 (s, J = 247 Hz).

Anal. Calcd. for $C_{16}H_{12}Br_2F_2O$: C, 45.96; H, 2.89; Br, 38.22. Found: C, 45.80; H, 3.10; Br, 37.86.

trans-1,4-Dibromo-2,3-epoxy-2,3-diphenylbutane (**7a**).

This compound was prepared in a similar manner (94% yield) as for **7b**, mp 125-126°; ir (potassium bromide): 1450, 950, 790, 700 cm^{-1} ; pmr (deuteriochloroform): δ 3.17 (d, J = 13 Hz, 2H), 3.58 (d, J = 13 Hz, 2H), 7.4-7.65 (m, 10H); ms: 303 (M-Br, 20), 301 (21), 201 (48), 199 (35), 105 (47), 103 (72), 102 (26), 77 (100), 51 (30); pmr (deuteriochloroform): δ 36.44, 71.88, 127.34, 128.52, 128.67, 135.26.

Anal. Calcd. for $C_{16}H_{14}Br_2O$: C, 50.29; H, 3.69; Br, 41.82. Found: C, 50.43; H, 3.79; Br, 41.83.

trans-2,3-Epoxy-1,4-di(imidazol-1-yl)-2,3-diphenylbutane (**8a**).

Sodium hydride (55% in mineral oil) (0.43 g, 0.01 mole) was added portionwise to an stirred solution of imidazole (0.63 g, 0.01 mole) and anhydrous dimethoxyethane (40 ml). The mixture was stirred at room temperature for 30 minutes. Compound **7a** (1.71 g, 4.47 moles) in anhydrous dimethoxyethane (10 ml) was then added dropwise. The mixture was refluxed for 4 hours, poured into ice-water and partitioned with dichloromethane. The organic layer was dried and evaporated. The residue was recrystallized from ethanol to afford **8** (0.91 g, 57%), mp 185-188°; ir (potassium bromide): 1510, 1230, 1080, 710 cm^{-1} ; pmr (deuteriochloroform): δ 3.62 (d, J = 14 Hz, 2H), 4.29 (d, J = 14 Hz, 2H), 6.59 (s, 2H), 6.85 (s, 2H), 7.00 (s, 2H), 7.3-7.45 (m, 10H); cmr (deuteriochloroform): δ 51.38, 69.98, 119.27, 126.39, 128.90, 129.04, 133.97, 137.32.

Anal. Calcd. for $C_{22}H_{20}N_4O$: C, 74.14; H, 5.66; N, 15.72. Found: C, 74.12; H, 5.70; N, 15.70.

trans-2,3-Epoxy-2,3-bis(fluorophenyl)-1,4-di(1,2,4-triazol-1-yl)butane (**9b**).

A solution of product **7b** (4.8 g, 11.4 mmoles) in acetonitrile (50 ml) was added dropwise on a refluxing mixture of 1,2,4-triazole (3.16 g, 46 mmoles), potassium carbonate (6.32 g, 46 mmoles) and acetonitrile (110 ml). The mixture was refluxed for 2 days, filtered and the solvent evaporated, the residue was partitioned between water and dichloromethane. The organic layer was washed with water dried and evaporated to give an oil that treated with ether separated 2.88 g of a solid (64%). The solid recrystallized from ethanol-ether afforded **9b**, mp 181-183°; ir (potassium bromide): 1510, 1280, 1230, 1140, 850 cm^{-1} ; pmr (deuteriochloroform): δ 3.93 (d, J = 14 Hz, 2H), 4.48 (d, J = 14 Hz, 2H), 6.95-7.45 (m, 8H), 7.74 (s, 2H), 7.80 (s, 2H); pmr (DMSO- d_6): δ 52.76, 68.33, 114.65 and 115.73 (d, J = 20 Hz), 129.08 and 129.51 (d, J = 7 Hz), 130.03 and 130.18 (d, J = 3 Hz), 144.52, 151.30, 155.79 and 167.95 (d, J = 240 Hz); ms: 394 (M, 11), 312 (27), 230 (24), 134 (28), 123 (95), 121 (66), 109 (41), 101 (44), 95 (100), 75 (31), 55 (29).

Anal. Calcd. for $C_{20}H_{16}F_2N_6O$: C, 60.90; H, 4.09; N, 21.31. Found: C, 61.02; H, 4.10; N, 21.40.

trans-2,3-Epoxy-2,3-diphenyl-1,4-di(1,2,4-triazol-1-yl)butane (**9a**).

This compound was prepared in a similar manner (37% yield) as for **9b**, mp 161-163°; ir (potassium bromide): 1280, 1140, 1020, 700 cm^{-1} ; pmr (deuteriochloroform): δ 3.93 (d, J = 14.5 Hz, 2H), 4.60 (d, J = 14.5 Hz, 2H), 7.40 (deceptive s, 10H), 7.74 (s, 2H), 7.78 (s, 2H); cmr (deuteriochloroform): δ 53.91, 69.44, 126.70, 128.92, 129.07, 133.51, 143.55, 151.61.

Anal. Calcd. for $C_{20}H_{16}N_6O$: C, 67.02; H, 5.06; N, 23.45. Found: C, 67.07; H, 5.28; N, 23.05.

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